DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Denver District Office
Building 20 – Denver Federal Center
P.O. Box 25087
Denver, Colorado 80225-0087
TELEPHONE: 303-236-3000

March 21, 2000

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Kenneth F. Yontz
President/CEO
Sybron International Corporation
411 East Wisconsin Ave., 24th Floor
Milwaukee, Wisconsin 53202

Ref #: DEN-00-23

Dear Mr. Yontz:

During an inspection of Metrex Research Corporation, 1270 S. Dransfeldt Rd., Parker, CO, conducted February 7 - 25, 2000, Consumer Safety Officer Nicholas R. Nance determined your firm manufactures glutaraldehyde-based high-level liquid sterilants and disinfectants. These products are devices within the meaning of Section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act).

The above-stated inspection revealed these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for the manufacturing, packing, storage, or installation are not in conformance with the Quality System Regulation (QSR), as specified in Title 21, Code of Federal Regulations, Part 820 (21 CFR 820) as follows:

1. Failure to establish and maintain procedures for finished device acceptance to ensure each production run, lot, or batch of finished devices meets acceptance criteria as required by 21 CFR 820.80(d). For example:

   a. The procedure being used for final release, [illegible] (SOP [illegible]), requires final testing of glutaraldehyde products using samples from the filling nozzle/heads immediately prior to bottling. This procedure is inadequate in that it requires pH and refractive index testing but does not require nor assure verification of glutaraldehyde concentration, specific gravity and foam testing at the time of finished packaging.

b. There is no record of the actual/numerical test results of the above mentioned pH and refractive index results.

c. SOP [illegible] requires only one sample from the filling head before bottling an entire lot of sterilant. There is no documented statistical rationale for this single sampling procedure considering that filling operations have occasionally required multiple days for a single lot of product.

2. Failure to adequately validate, with a high degree of assurance, production processes where results cannot be fully verified by subsequent inspection and testing as required by 21 CFR 820.75(a). For example:

a. The complete Procide manufacturing process has not been validated nor qualified.

b. The Procide 45-minute immersion high-level disinfection label claim has not been validated.

c. Process validation SOP[illegible] states revalidation will be performed when "[illegible]" are made or after "[illegible]". There is no criteria established to evaluate or define these events.

d. The Procide stability and expiration dating system has not been validated.

e. Validation of the deionized (DI) water system, performed 5/99, did not include assurances that water being used in production met pre-established microbial colony forming units (CFU) limits, or justification supporting current CFU microbial load specifications, microbiological testing procedures and schedules.

3. Failure to investigate the cause of nonconformities relating to product, processes, and the quality system as required by 21 CFR 820.100(a)(2). For example:

a. pH and refractive index test failures found at final testing are not investigated to determine root causes before product release.

b. QA analysis sheets for some sterilants tested for shelf-life/stability show pH and glutaraldehyde concentrations below minimum specifications before their assigned product expiration dates. There is no evidence these failures were investigated.

c. Discrepancy Report [illegible] reported DI water CFU limits had been exceeded. There is no evidence of a failure investigation nor that system revalidation and/or maintenance was considered.

4. Failure to implement appropriate statistical methods where necessary to detect recurring quality problems as required by 21 CFR 820.100(a)(1). For example:

a. Metrex procedures do not require nor assure the performance of statistical analyses of Discrepancy Reports and Change Orders, nor define the methods to be used in the analyses of quality data.

b. Discrepancy Reports, Corrective Action Requests and Change Orders are not prioritized, trended or evaluated for significance and risk.

5. Failure to verify or validate Corrective and Preventive Actions to ensure such actions are effective and do not adversely affect the finished device as required by 21 CFR 820.100(a)(4). For example, corrective actions and change orders are not monitored nor tracked to assure they are appropriately implemented in a timely manner.

6. Failure to document Corrective and Preventive Action activities as required by 21 CFR 820.100(b). For example, there is no documented justification supporting decisions to not perform failure investigations in follow-up to Discrepancy Reports.

7. Failure to establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure the product meets its current approved specifications as required by 21 CFR 820.90(b)(2). For example, when product is reworked/reprocessed, procedures do not assure the reworked product is re-inspected to assure it meets all Device Master Record product specifications and claimed effectivity.

8. Failure of management with executive responsibility to review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure the quality system satisfies established quality policy and objectives, as required by 21 CFR 820.20(c). For example, management reviews do not include quality trends of Discrepancy Reports, Corrective/Preventive Actions nor Change Orders.

We acknowledge receipt and have thoroughly reviewed your March 9, 2000 response to the FD-483. Several of your proposed corrections, if fully implemented, appear to adequately address some of our concerns and will be evaluated during the next inspection. However, as described below, some of your proposed corrections are not adequate and/or need further clarification.

In response to FD-483 observation #1, Metrex has implemented SOP [illegible] which requires complete testing of [illegible] container of product from the [illegible] and [illegible] from the [illegible] Based on the information you have provided, your response is inadequate. What is the statistical rationale for this sampling plan? During the inspection it was noted that filling operations might span several days from blending of the bulk solution to completion of packaging. What assurance do you have that daily variations are not occurring during this extended filling operation?

Metrex SOP [illegible] includes 23 attachments, which are product specific and will be used as QA analysis sheets to document finished product analysis. These attachments include [illegible]

and We assume a separate analysis sheet will be used for each of the 1-gallon containers rather than a single analysis sheet for both containers and averaging the results. Is this the case?

Metrex SOP was submitted in support of your response to FD-483 observation #2. Item 3.4 of this SOP states that a will be performed if the production line will sit idle for an extended period of time. Please clarify what is meant by an extended period of time.

Your response to FD-483 observation #3 states that the QA analysis sheets reviewed by the investigator did not show any glutaraldehyde concentration to be below minimum specifications. You are referring to the average results while the investigator was referring to individual test results, which did show concentrations below minimum specification. One of the lot numbers was misstated on the FD-483 as lot #22191L. The correct lot number is 22191C.

Your response to FD-483 observation #3 also states that Metrex has initiated a formal project, , to determine the root cause of out-of-specification findings in unactivated product. A corrective action item for this includes a proposal to revise the unactivated range. We trust your validation to support a change in specifications will be very thorough and well documented.

Your response to FD-483 observation #4 states that Metrex believes the entire Procide manufacturing process has been validated. We disagree. Documents reviewed by the investigator during the inspection show portions of the manufacturing process have been validated. The dates of these validations vary widely. The entire process, operating at once, has not been validated. In addition, we question the effectiveness of your validation of portions of your process. For example, numerous lots of product have been released for filling based on analysis of the bulk solution, only to fail pH testing at the filling line. This raises serious questions about your filling, cleaning and/or blending processes that this problem continues to occur. Further, sampling and testing are performed only on the first day of bottling, even if bottling of the lot requires several days to complete. There is no validation that justifies this procedure nor the practice of holding bulk solution for extended periods of time prior to filling.

Your response to FD-483 item #4 further states that Metrex is reviewing its current shelf life claim and will revise it to one year pending microbial efficacy. What steps are you taking to assure that product currently in distribution channels with a labeled expiration date of 2 years continues to meet its specifications?

We agree with your decision to suspend production and distribution of all Procide products until the 45-minute immersion high-level disinfection label claim is validated.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA-483 issued at the closeout of the inspection (copy enclosed) may be symptomatic of serious underlying problems in your firm's manufacturing and

quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

You should take prompt action to correct these and any other manufacturing or quality systems deviations identified by your internal audits. Failure to promptly correct these deviations may be identified in a follow-up inspection, and may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within 15 days of receipt of this letter, of any additional steps you will be taking to achieve compliance, which have not been previously reported to us.

Your reply should be sent to the Food and Drug Administration, Denver District Office, Attention: H. Tom Warwick, Compliance Officer, at the above address.

Sincerely,

Karen S. Kreuzer

Karen S. Kreuzer
Acting District Director

Cc: [redacted]

[redacted]

Mr. Ruben L. Kembel, Plant Manager
Metrex Research Corporation
10270 S. Dransfeldt Road
Parker, CO 81034

Enclosure:
As Stated